

Seizure 2002; 11: 47–50

doi:10.1053/seiz.2001.0571, available online at <http://www.idealibrary.com> on 

Role of topiramate in adults with intractable epilepsy, mental retardation, and developmental disabilities

BALDEV K. SINGH & SHERYL WHITE-SCOTT

Departments of Neurology and Medicine, New York Medical College, Westchester Institute for Human Development, Valhalla, NY, USA

Correspondence to: Baldev K. Singh, MD, Director, Adult Neurology, Westchester Institute for Human Development, Cedarwood Hall, Valhalla, NY 10595-1080, USA. *E-mail:* baldev_singh@nymc.edu

The efficacy and safety of topiramate in patients with intractable mixed seizures, mental retardation (MR), and developmental disabilities (DD) were investigated. Twenty patients (eight females and 12 males) aged 21–57 years old with intractable epilepsy with mixed seizures, MR [profound (five), severe (three), moderate (two), mild (eight) and borderline (two)], and DD were treated with adjunctive topiramate 25 mg per day for 1 week followed by titration to clinical response (range 50–350 mg per day). Other antiepileptic drugs (AEDs) were decreased simultaneously. Topiramate therapy was discontinued in four patients for adverse events consisting of disorientation, unsteadiness, and pneumonia (one patient); anaphylactic shock from a tuna fish allergy (one); patient choice (one); and loss to follow-up (one). Seizures improved by $\geq 50\%$ in 11 of 16 patients (69%). Two patients (13%) were seizure free, including one patient who prior to topiramate therapy was seizure free but experiencing an intolerable adverse effect during therapy with another AED. Seizure duration and/or severity decreased in seven patients (44%). An increase in alertness was observed in 11 patients (59%). Topiramate was associated with improvement in seizure severity and alertness in this series and may be useful as adjunctive therapy in patients with mixed seizures, MR, and DD.

© 2002 BEA Trading Ltd

Key words: topiramate; epilepsy; mental retardation; developmental disabilities; seizures.

INTRODUCTION

Epilepsy is a co-existing neurological disorder in 40–50% of individuals with mental retardation (MR) and developmental disabilities (DD). Many of these patients have seizures that are not controlled satisfactorily with their current antiepileptic drug (AED) therapy. For example, in a chart review of 100 patients with MR, DD, and intractable seizures, we found that 40% of patients were still experiencing seizures despite treatment with two to three AEDs¹. Thus, a substantial number of patients with MR and DD could benefit from improved seizure control.

Topiramate has been shown to be effective as adjunctive therapy in a wide range of seizure types, including partial-onset seizures^{2–7}, seizures associated with Lennox–Gastaut syndrome⁸, and primary generalized tonic–clonic seizures⁹. Most commonly

reported side effects in the double-blind adjunctive therapy trials in adults with refractory partial onset seizures were related to the central nervous system and included somnolence, dizziness, abnormal thinking, fatigue, ataxia, confusion, paresthesia and impaired concentration¹⁰. Most adverse events with topiramate tended to appear early in the course of treatment and to resolve with continuing therapy. Cognitive and CNS adverse effects may occur less frequently with a lower initial dose of topiramate and slower titration¹¹.

It is uncertain whether patients with underlying static CNS dysfunction may be more, or less susceptible to potential CNS-related side effects of AEDs, or whether cognitive function will improve as a result of improved seizure control, or a reduction of total AED requirements. This evaluation was undertaken to determine the usefulness of topiramate in individuals with intractable mixed seizures, MR, and DD.

METHOD

Patients

Study patients were selected based on a chart review of 368 epilepsy patients who were ≥ 21 years of age, had MR and DD, and were being treated at the neurology clinic of the Westchester Institute for Human Development. Severity of mental retardation was determined through a combination of IQ scores and psychological evaluation and was graded as profound, severe, moderate, mild, or borderline. Eligible patients had the following entry criteria: mixed seizures (i.e. mixed generalized seizures or mixed partial and generalized seizures) that were uncontrolled by treatment with standard or newer AEDs; or intolerable adverse effects with current AED therapy. Seizure episodes were classified according to guidelines for seizure classification of the International League Against Epilepsy¹². Patients with a history of renal stones were excluded. The study protocol was approved by the institutional review board, and written informed consent was obtained from patients or their guardians prior to study entry.

Procedure

Topiramate therapy initially was given in addition to baseline AEDs at a dosage of 25 mg per day for 1 week. The topiramate dosage was then increased to a level that was dependent on seizure frequency and tolerability. Concomitant baseline AEDs were gradually withdrawn when appropriate. Based on data forms completed by patients and/or care givers, the following were monitored during topiramate therapy: seizure occurrence (time, type, and duration of seizures); adherence to AED therapy; adverse events; precipitants of seizures; and the number of emergency room visits and the treatment provided in the emergency room. At the final study visit, investigator's and patients' global evaluations of overall improvement were recorded. The investigator rated improvement as worse, none, minimal, moderate, or marked; and patients assessed their improvement as poor, fair, good, or excellent. Based on physician's evaluations during clinic visits and information from care givers, adverse events were determined. During study visits, patients and/or care givers were asked specifically about patient alertness. Clinical laboratory tests (i.e. AED plasma levels, CBC, and serum electrolytes) were performed during the first 2–4 weeks of topiramate therapy and then every 3 months thereafter.

RESULTS

Twenty patients (eight females and 12 males) entered the study and were treated with topiramate. Demographic characteristics of these patients are presented in Table 1. The age of the patients ranged from 21–57 years old. The level of mental retardation was: profound in five patients, severe in three, moderate in two, mild in eight, and borderline in two. The seizures experienced by these patients were uncontrolled on various combinations of phenytoin, carbamazepine, phenobarbital, primidone, lamotrigine, or divalproate sodium.

Table 1: Patient characteristics.

Variable	
N	20
Age	21–57 years
Gender	
Female	8
Male	12
Baseline seizure frequency	
Median	4.5/month
Range	0–20/month
Seizure type, N (%)	
Generalized tonic-clonic	19 (95%)
Partial complex	16 (80%)
Atonic	8 (40%)
Tonic	7 (35%)
Clonic	6 (30%)
Myoclonic	3 (15%)
Drop attacks	2 (10%)
Absence	1 (5%)
Mental retardation, N (%)	
Profound	5 (25%)
Severe	3 (15%)
Moderate	2 (10%)
Mild	8 (40%)
Borderline	2 (10%)
Baseline AEDs	
1 AED	5%
2 AEDs	55%
3 AEDs	40%

Four patients discontinued topiramate treatment during the study for reasons presented in Table 2. Among the 16 patients completing the trial, the mean dosage of topiramate was 189 mg per day (range 50–350 mg per day) and the mean duration of therapy was 42 weeks (range 20–54 weeks). Seizure frequency was reduced by $\geq 50\%$ in 11 of 16 patients (69%) and two patients were seizure free (13%) (Fig. 1). There was no change in seizure frequency in three patients, including one patient who was seizure-free at baseline (but experiencing intolerable adverse effects while on other AED therapy) and remained seizure-free during topiramate therapy, and seizures increased in two patients. Seizure duration and/or severity was reduced in seven patients (44%). Global evaluations of improvement were obtained in 18 patients. Based on investigator global evaluations, improvement was

marked to moderate in 15 patients and none to minimal in three patients. Overall improvement was rated as excellent by 13 patients, fair to good by one patient and poor to fair or fair by four patients.

Table 2: Treatment discontinuations.

Reason	N
Adverse events (disorientation, unsteadiness, pneumonia)	1
Anaphylactic shock (allergy to tuna fish)	1
Patient choice	1
Lost to follow-up	1

The concomitant AEDs before and after topiramate therapy are listed in Table 3 for the 16 patients who completed the study. In 11 patients (69%) at least one baseline AED was discontinued. Reductions in baseline AED dosages were achieved in 13 patients. Improved alertness was evidenced in 11 of 16 patients (69%). The emergency room visits for seizures did not increase or decrease. Adverse events noted during the study are presented in Table 4. None of the adverse events were serious although one patient discontinued topiramate (see Table 2 for treatment discontinuations).

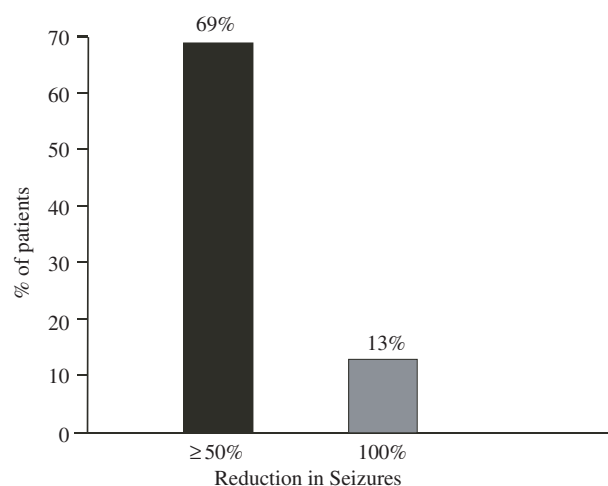


Fig. 1: Percentages of patients achieving a $\geq 50\%$ reduction from baseline in the average monthly rate of seizures or seizure freedom.

Table 3: Concomitant antiepileptic drugs in the 16 patients completing the study.

	Number of patients	
	Before topiramate	After topiramate
Valproate	9	7
Phenytoin	6	6
Carbamazepine	8	5
Lamotrigine	5	2
Gabapentin	4	0
Phenobarbital/primidone	4	3

Table 4: Adverse events.

Adverse event	N
Behavior problem	3
Decreased alertness	3
Drowsiness	1
Increase in seizures	1
Abnormal movements (due to valproate)	1
Disorientation, unsteadiness, pneumonia	
Low platelets	1
Low WBC	1

DISCUSSION

In the present study, topiramate as adjunctive therapy resulted in clinically significant improvement in seizure control (a reduced seizure frequency of $\geq 50\%$) in 69% of adults with MR, DD, and intractable mixed seizures that were not satisfactorily controlled with other AEDs. Two patients (13%) were seizure free, including one patient who was seizure free before admission to this study but experienced an intolerable adverse effect while on previous AED treatment. In addition, the duration and/or severity of seizures was reduced in 44% of patients. In comparison, five multicenter placebo-controlled trials of topiramate as adjunctive therapy for partial-onset seizures in adults demonstrated $\geq 50\%$ reductions from baseline in partial-onset seizure rates in 41% (146/360) of patients treated with topiramate compared to 10% (17/174) of placebo-treated patients²⁻⁷. Four percent of topiramate-treated patients became seizure free while no patients treated with placebo became seizure free. Similarly, in a multicenter placebo-controlled study in adults and children with generalized tonic-clonic seizures, the seizure rates decreased from baseline by $\geq 50\%$ in 56% (22/39) of the topiramate group and in 20% (8/40) of the placebo group and 13% (5/39) of topiramate-treated patients became seizure free vs. 5% (2/40) of placebo-treated patients⁸.

In this study, a high level of seizure control was obtained with minimal incidence of adverse events. Although topiramate has been associated with CNS side effects, topiramate at doses of 50–350 mg per day was well tolerated in this trial with few discontinuations due to adverse events. Topiramate appears to be both safe and effective as an add-on therapy in patients with MR and DD, who have not achieved satisfactory control of their mixed seizures with other currently marketed AEDs.

EDITOR'S NOTE

The use of the term mental retardation is not current practice in UK writings, but is perfectly acceptable in the USA, so I have kept the term in this paper, and not altered it.

REFERENCES

1. Singh, B. K. and Towle, P. O. Antiepileptic drug status in adult outpatients with mental retardation. *American Journal on Mental Retardation* 1993; **98** (Suppl. 1): 41–46.
2. Ben-Menachem, E., Henriksen, O., Dam, M., Mikkelsen, M. *et al.* Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia* 1996; **37**: 539–543.
3. Faught, E., Wilder, B. J., Ramsay, R. E. *et al.* Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400- and 600-mg daily dosages. *Neurology* 1996; **46**: 1684–1690.
4. Privitera, M., Fincham, R., Penry, J. *et al.* Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000-mg daily dosages. *Neurology* 1996; **46**: 1678–1683.
5. Sharief, M., Viteri, C., Ben-Menachem, E. *et al.* Double-blind, placebo-controlled trial of topiramate in patients with refractory epilepsy. *Epilepsy Research* 1996; **25**: 217–224.
6. Tassinari, C. A., Michelucci, R., Chauvel, P. *et al.* Double-blind, placebo-controlled trial of topiramate (600 mg daily) for the treatment of refractory partial epilepsy. *Epilepsia* 1996; **37**: 763–768.
7. Elterman, R. D., Glauser, T. A., Wyllie, E. *et al.* A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. *Neurology* 1999; **52**: 1338–1344.
8. Biton, V., Montouris, G. D., Ritter, F. *et al.* A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. *Neurology* 1999; **52**: 1330–1337.
9. Sachdeo, R. C., Glauser, T. A., Ritter, F. *et al.* A double-blind, randomized trial of topiramate in Lennox–Gastaut syndrome. *Neurology* 1999; **52**: 1882–1887.
10. Shorvon, S. D. Safety of topiramate: adverse events and relationships to dosing. *Epilepsia* 1996; **37** (Suppl. 2): S18–S22.
11. Sander, J. W. A. S. Practical aspects of the use of topiramate in patients with epilepsy. *Epilepsia* 1997; **38** (Suppl. 1): S56–S58.
12. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981; **22**: 489–501.